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(54) Title: RENIN INHIBITORS HAVING A LACTAM PSEUDO DIPEPTIDE

(57) Abstract

Novel renin-inhibiting peptides of the formula X-A₆-B₇-C₈-D₉-E₁₀-F₁₁-G₁₂-H₁₃-I₁₄-Z, having a lactam pseudo dipeptide at C₈-D₉ positions, X and Z are terminal groups, and the remaining variables are absent or are amino acid residues. Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension.

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RENIN INHIBITORS HAVING A LACTAM PSEUDO DIPEPTIDE
DESCRIPTION

BACKGROUND OF THE INVENTION

The present invention provides novel compounds. More particularly, the present invention provides novel renin-inhibiting peptide analogs. Most particularly, the present invention provides renin-inhibitory compounds having a lactam pseudo dipeptide at positions 8 and 9 as compared to the renin substrate. The renin inhibitors provided herein are useful for the diagnosis and control of renin-dependent hypertension.

Renin is an endopeptidase which specifically cleaves a particular peptide bond of its substrate (angiotensinogen), of which the N-terminal sequence in equine substrate is for example:

Renin
↓
15 Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser- IA
1 2 3 4 5 6 7 8 9 10 11 12 13 14

as found by L.T. Skeggs et al, J. Exper. Med. 106, 439 (1957). Human renin substrate has a different sequence as recently discovered by D.A. Tewkesbury et al, Biochem. Biophys. Res. Comm. 99, 1311 (1981). It may be represented as follows:

Renin
↓
25 -Val-Ile-His- IB
11 12 13

and having the sequence to the left of the arrow (↓) being as designated in formula IA above.

30 Renin cleaves angiotensinogen to produce angiotensin I, which is converted to the potent pressor angiotensin II. A number of angiotensin I converting enzyme inhibitors are known to be useful in the treatment of hypertension. Inhibitors of renin are also useful in the treatment of hypertension.

35 INFORMATION DISCLOSURE

A number of renin-inhibitory peptides have been disclosed. Thus, U.S. patent 4,424,207, and European published applications 45,665 and 104,041 disclose certain peptides with the dipeptide at the 10,11-position containing an isopeptide bond. A number of statine derivatives

stated to be renin inhibitors have been disclosed, see, e.g., European published applications 77,028; 81,783; and 114,993; and U.S. patents 4,478,826; 4,470,971 and 4,479,941. Terminal disulfide cycles have also been disclosed in renin inhibiting peptides; see, e.g., U.S. patents 4,477,440 and 4,477,441. Aromatic and aliphatic amino acid residues at the 10,11 position of the renin substrate are disclosed in U.S. patent 4,478,827. C-terminal amide cycles are disclosed in U.S. patent 4,485,099. Certain tetrapeptides are disclosed in European publications 111,266 and 77,027. Further, European published application No. 118,223 discloses certain renin inhibiting peptide analogs where the 10-11 peptide link is replaced by a one to four atom carbon or carbon-nitrogen link. Additionally, Holladay et al., in "Synthesis of Hydroxyethylene and Ketomethylene Dipeptide Isosteres", Tetrahedron Letters, Vol. 24, No. 41, pp. 4401-4404, 1983 disclose various intermediates in a process to prepare stereo-directed "ketomethylene" and "hydroxyethylene" dipeptide isosteric functional groups disclosed in the above noted U.S. Patent No. 4,424,207.

Additionally, published European Applications 45,161 and 53,017 disclose amide derivatives useful as inhibitors of angiotensin converting enzymes.

SUMMARY OF THE INVENTION

The present invention particularly provides a renin inhibitory peptide of the formula $X-A_6-B_7-C_8-D_9-E_{10}-F_{11}-G_{12}-H_{13}-I_{14}-Z$,

wherein X is

- 25 (a) hydrogen,
- (b) C_1-C_5 alkyl
- (c) $R_5-O-CH_2-C(O)-$,
- (d) $R_5-CH_2-O-C(O)-$,
- (e) $R_5-O-C(O)-$,
- 30 (f) $R_5-(CH_2)_n-C(O)-$,
- (g) $R_4N(R_4)-(CH_2)_n-C(O)-$,
- (h) $R_5-SO_2-(CH_2)_q-C(O)-$,
- (i) $R_5-SO_2-(CH_2)_q-O-C(O)-$, or
- (j) $R_6-(CH_2)_i-C(O)-$;

35 wherein A_6 is absent or a divalent moiety of the formula XL_1 , XL_2 , or XL_{2a}

wherein B_7 is absent or a divalent moiety of the formula XL_b

wherein C_8-D_9 is XL_3 or XL_{3a} , or

wherein C₈-D₉ is a monovalent moiety of the formula XL_{3b} when X,
A₆, and B₇ are absent;

wherein E₁₀-F₁₁ is a divalent moiety of the formula XL₆, XL_{6a},
XL_{6b}, XL_{6c}, XL_{6d} or XL_{6e};

5 wherein * indicates an asymmetric center which is either in the R
or S configuration;

wherein G₁₂ is absent or a divalent moiety of the formula XL₄ or
XL_{4a};

wherein H₁₃ is absent or a divalent moiety of the formula XL₄;

10 wherein I₁₄ is absent or a divalent moiety of the formula XL₅;

wherein Z is

- (a) -O-R₁₀,
- (b) -N(R₄)R₁₄, or
- (c) C₄-C₈cyclic amino;

15 wherein R is

- (a) isopropyl,
- (b) isobutyl,
- (c) phenylmethyl, or
- (d) C₃-C₇cycloalkyl;

20 wherein R₁ is

- (a) hydrogen,
- (b) C₁-C₅alkyl,
- (c) aryl,
- (d) C₃-C₇cycloalkyl,
- (e) -Het,
- (f) C₁-C₃alkoxy, or
- (g) C₁-C₃alkylthio;

wherein R₂ is

- (a) hydrogen, or
- (b) -CH(R₃)R₄;

30 wherein R₃ is

- (a) hydrogen,
- (b) hydroxy,
- (c) C₁-C₅alkyl,
- (d) C₃-C₇cycl alkyl,
- (e) aryl,
- (f) -Het,
- (g) C₁-C₃alkoxy, or

-4-

(h) C_1 - C_3 alkylthio;wherein R_4 at each occurrence is the same or different and is

(a) hydrogen, or

(b) C_1 - C_5 alkyl;5 wherein R_5 is(a) C_1 - C_6 alkyl.(b) C_3 - C_7 cycloalkyl,

(c) aryl,

(d) -Het, or

10 (e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1 - C_5 alkyl,(c) $-(CH_2)_p$ -aryl,15 (d) $-(CH_2)_p$ -Het,(e) $-(CH_2)_p$ - C_3 - C_7 cycloalkyl,

(f) 1- or 2-adamantyl,

(g) -S-aryl,

(h) -S- C_3 - C_7 cycloalkyl, or20 (i) -S- C_1 - C_6 -alkyl;wherein R_7 is

(a) hydrogen,

(b) C_1 - C_5 alkyl,

(c) hydroxy,

25 (d) amino C_1 - C_4 alkyl-,(e) guanidinyl C_1 - C_3 alkyl-,

(f) aryl,

(g) -Het,

(h) methylthio,

30 (i) $-(CH_2)_p$ - C_3 - C_7 cycloalkyl, or

(j) amino;

wherein R_8 is

(a) hydrogen,

(b) C_1 - C_5 alkyl,

35 (c) hydroxy,

(d) aryl,

(e) -Het,

(f) guanidinyl C_1 - C_3 alkyl-, or

(g) $-(CH_2)_p-C_3-C_7$ cycloalkyl;

wherein R_9 is

- (a) hydrogen,
- (b) hydroxy,
- 5 (c) amino C_1-C_4 alkyl-, or
- (d) guanidinyl C_1-C_3 alkyl-;

wherein R_{10} is

- (a) hydrogen,
- (b) C_1-C_5 alkyl,
- 10 (c) $-(CH_2)_nR_{16}$,
- (d) $-(CH_2)_nR_{17}$,
- (e) C_3-C_7 cycloalkyl,
- (f) a pharmaceutically acceptable cation,
- (g) $-CH(R_{25})-CH_2-R_{15}$, or
- 15 (h) $-CH_2-CH(R_{12})-R_{15}$;

wherein R_{11} is -R or -R₂;

wherein R_{12} is $-(CH_2)_n-R_{13}$;

wherein R_{13} is

- (a) aryl,
- 20 (b) amino,
- (c) mono-, di or tri- C_1-C_3 alkylamino,
- (d) -Het,
- (e) C_1-C_5 alkyl
- (f) C_3-C_7 cycloalkyl,
- 25 (g) C_2-C_5 alkenyl,
- (h) C_3-C_7 cycloalkenyl,
- (i) hydroxy,
- (j) C_1-C_3 alkoxy,
- (k) C_1-C_3 alkanoyloxy,
- 30 (l) mercapto,
- (m) C_1-C_3 alkylthio,
- (n) -COOH,
- (o) -CO-O- C_1-C_6 alkyl,
- (p) -CO-O-CH₂-(C_1-C_3 alkyl)-N(C_1-C_3 alkyl)₂,
- 35 (q) -CO-NR₂₂R₂₆;
- (r) C_4-C_7 cyclic amino,
- (s) C_4-C_7 cycloalkylamino,
- (t) guanidyl.

- (u) cyano,
- (v) N-cyanoguanidyl,
- (w) cyanoamino,
- (x) (hydroxy C₂-C₄alkyl)amino, or
- 5 (y) di-(hydroxyC₂-C₄alkyl)amino;

wherein R₁₄ is

- (a) hydrogen,
- (b) C₁-C₁₀alkyl,
- (c) -(CH₂)_n-R₁₈,
- 10 (d) -(CH₂)_n-R₁₉,
- (e) -CH(R₂₅)-CH₂-R₁₅,
- (f) -CH₂-CH(R₁₂)-R₁₅,
- (g) (hydroxy C₁-C₈alkyl), or
- (h) (C₁-C₃alkoxy)C₁-C₈alkyl;

15 wherein R₁₅ is

- (a) hydroxy,
- (b) C₃-C₇cycloalkyl,
- (c) aryl,
- (d) amino,
- 20 (e) mono-, di-, or tri- C₁-C₃alkylamino,
- (f) mono- or di-[hydroxy C₂-C₄alkyl]amino,
- (g) -Het,
- (h) C₁-C₃alkoxy-,
- (i) C₁-C₃alkanoyloxy-,
- 25 (j) mercapto,
- (k) C₁-C₃alkylthio-,
- (l) C₁-C₅alkyl,
- (m) C₄-C₇cyclic amino,
- (n) C₄-C₇cycloalkylamino,
- 30 (o) C₁-C₅alkenyloxy,
- (p) C₃-C₇cycloalkenyl;

wherein R₁₆ is

- (a) aryl,
- (b) amino,
- 35 (c) mono- or di- C₁-C₃alkylamino,
- (d) hydroxy,
- (e) C₃-C₇cycloalkyl,
- (f) C₄-C₇cyclic amin, or

(g) C_1 - C_3 alkanoyloxy;

wherein R_{17} is

- (a) -Het,
- (b) C_2 - C_5 alkenyl,
- 5 (c) C_3 - C_7 cycloalkenyl,
- (d) C_1 - C_3 alkoxy,
- (e) mercapto,
- (f) C_1 - C_3 alkylthio,
- (g) -COOH,
- 10 (h) -CO-O- C_1 - C_6 alkyl,
- (i) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
- (j) -CO-NR₂₂R₂₆,
- (k) tri- C_1 - C_3 alkylamino,
- (l) guanidyl,
- 15 (m) cyano,
- (n) N-cyanoguanidyl,
- (o) (hydroxy C_2 - C_4 alkyl)amino,
- (p) di-(hydroxy C_2 - C_4 alkyl)amino, or
- (q) cyanoamino;

20 wherein R_{18} is

- (a) amino,
- (b) mono-, or di- C_1 - C_3 alkylamino,
- (c) C_4 - C_7 cyclic amino; or
- (d) C_4 - C_7 cycloalkylamino;

25 wherein R_{19} is

- (a) aryl,
- (b) -Het,
- (c) tri- C_1 - C_3 alkylamino,
- (d) C_3 - C_7 cycloalkyl,
- 30 (e) C_2 - C_5 alkenyl,
- (f) C_3 - C_7 cycloalkenyl,
- (g) hydroxy,
- (h) C_1 - C_3 alkoxy,
- (i) C_1 - C_3 alkanoyloxy,
- (j) mercapto,
- (k) C_1 - C_3 alkylthio,
- (l) -COOH,
- (m) -CO-O- C_1 - C_6 alkyl,

(n) $-\text{CO}-\text{O}-\text{CH}_2-(\text{C}_1\text{-}\text{C}_3\text{alkyl})-\text{N}(\text{C}_1\text{-}\text{C}_3\text{alkyl})_2$,
(o) $-\text{CO}-\text{NR}_{22}\text{R}_{26}$,
(p) guanidyl,
(q) cyano,
5 (r) N-cyanoguanidyl,
(s) cyanoamino,
(t) (hydroxy $\text{C}_2\text{-}\text{C}_4$ alkyl)amino,
(u) di-(hydroxy $\text{C}_2\text{-}\text{C}_4$ alkyl)amino; or
(v) $-\text{SO}_3\text{H}$;

10 wherein R_{20} is
(a) hydrogen,
(b) $\text{C}_1\text{-}\text{C}_5$ alkyl, or
(c) aryl- $\text{C}_1\text{-}\text{C}_5$ alkyl;
wherein R_{21} is
15 (a) $-\text{NH}_2$, or
(b) $-\text{OH}$;
wherein R_{22} is
(a) hydrogen, or
(b) $\text{C}_1\text{-}\text{C}_3$ alkyl;
20 wherein R_{23} is
(a) $-(\text{CH}_2)_n-\text{OH}$,
(b) $-(\text{CH}_2)_n-\text{NH}_2$,
(c) aryl, or
(d) $\text{C}_1\text{-}\text{C}_3$ alkyl;
25 wherein R_{24} is
(a) $-\text{R}_1$,
(b) $-(\text{CH}_2)_n-\text{OH}$, or
(c) $-(\text{CH}_2)_n-\text{NH}_2$;
wherein R_{25} is
30 (a) hydrogen,
(b) $\text{C}_1\text{-}\text{C}_3$ alkyl; or
(c) phenyl- $\text{C}_1\text{-}\text{C}_3$ alkyl;
wherein R_{26} is
(a) hydrogen,
35 (b) $\text{C}_1\text{-}\text{C}_3$ alkyl, or
(c) phenyl- $\text{C}_1\text{-}\text{C}_3$ alkyl;
wherein m is one or two;
wherein for each occurrence n is independently an integer of zero

to five, inclusive;

wherein p is zero to 2 inclusive;

wherein q is 1 to 5, inclusive;

wherein Q is

5 (a) -CH₂-,
(b) -CH(OH)-,
(c) -O-, or
(d) -S-; and

wherein M is

10 (a) -CO-, or
(b) -CH₂-;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

15 (a) C₁-C₃alkyl,
(b) hydroxy,
(c) C₁-C₃alkoxy,
(d) halo,
(e) amino,
(f) mono- or di-C₁-C₃alkylamino,
20 (g) -CHO,
(h) -COOH,
(i) COOR₂₆,
(j) CONHR₂₆,
(k) nitro,
25 (l) mercapto,
(m) C₁-C₃alkylthio,
(n) C₁-C₃alkylsulfinyl,
(o) C₁-C₃alkylsulfonyl,
(p) -N(R₄)-C₁-C₃alkylsulfonyl,
30 (q) SO₃H,
(r) SO₂NH₂,
(s) -CN, or
(t) -CH₂NH₂;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3

-10-

of the following:

- (i) C_1 - C_6 alkyl,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- 5 (iv) C_1 - C_4 alkoxy,
- (v) halo,
- (vi) aryl,
- (vii) aryl C_1 - C_4 alkyl-,
- (viii) amino,
- 10 (ix) mono- or di- C_1 - C_4 alkylamino, and
- (x) C_1 - C_5 alkanoyl;

with the overall provisos that

(1) R_{18} or R_{19} is hydroxy, mercapto, or amino, or a mono-substituted nitrogen containing group bonded through the nitrogen only when n is not one;

(2) R_{12} is $-(CH_2)_n-R_{13}$ and n is zero and both R_{13} and R_{15} are oxygen-, nitrogen-, or sulfur-containing substituents bonded through the hetero atom, only when the hetero atom is not also bonded to hydrogen;

20 (3) R_{17} or R_{19} is $-COOH$ only when n for that moiety is other than zero;

(4) R_{16} or R_{17} is an amino-containing substituent, hydroxy, mercapto, or $-Het$ bonded through the hetero atom only when n for that substituent is an integer from two to five, inclusive;

25 (5) when R_{12} is $-(CH_2)_n-R_{13}$ and n is zero, then R_{13} and R_{15} cannot both be $-COOH$; and

(6) R_{17} or R_{19} is $-Het$, only when $-Het$ is other than cyclic amino;

30 or a carboxy-, amino-, or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid addition salt thereof.

These compounds are shown in relation to the human renin substrate as follows:

	6	7	8	9	10	11	12	13			
35	-His	Pro	Phe	His	Leu	Val	Ile	His-			
	X	A ₆	B ₇	C ₈	D ₉	E ₁₀	F ₁₁	G ₁₂	H ₁₃	I ₁₄	Z,

The present invention provides peptide inhibitors of renin which contain modification of positions C₈ and D₉. These modifications

involve the insertion of a lactam moiety at this position.

Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzene-sulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, 5 cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethane-sulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, 10 nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus 15 (C₁-C₄)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C₄-C₇cyclic amino indicates a monocyclic group containing one nitrogen and 4 to 7 carbon atoms.

20 Examples of (C₃-C₁₀)cycloalkyl which include alkyl-substituted cycloalkyl containing a total of up to 10 total carbon atoms, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, cyclohexyl, 25 cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and isomeric forms thereof.

Examples of aryl include phenyl, naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, 30 (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4-, 2,3,6-, or 2,4,5-)trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-)trifluoromethylphenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, 35 (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxy-phenyl, and 2,4-dichloro(5- or 6-)methylphenyl, and the like.

-12-

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl, indolyl, N^{in} -formyl-indolyl, $N^{in}C_1-C_5alkyl-C(0)-indolyl$, [1,2,4]-triazolyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-thienyl, piperidinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazol-5-idinyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted 10 as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

15 Halo is halogen (fluoro, chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include: pharmaco logically acceptable metal cations, ammonium, amine cations, or 20 quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, 25 or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), "Nomenclature and Symbolism for Amino Acids and 30 Peptides," Eur. J. Biochem. 138:9-37 (1984) unless otherwise indicated.

The renin inhibitors of this invention are useful for treating any medical condition for which it is beneficial to reduce the levels of active circulating renin. Examples of such conditions include renin-dependent hypertension, hypertension, hypertension under treatment with another antihypertensive and/or a diuretic agent, congestive heart failure, angina, and post-myocardial infarction. The renin-angiotension system may play a role in maintenance of intracellular home-

stasis: see Clinical and Experimental Hypertension, 86, 1739-1742 (1984) at page 1740 under Discussion.

The compounds of the present invention are preferably orally administered to humans to effect renin inhibition for the purpose of favorably affecting blood pressure. For this purpose, the compounds 5 are administered from 0.1 mg to 1000 mg per kg per dose, administered from 1 to 4 times daily. Equivalent dosages for other routes of administration are also employed.

The exact dose depends on the age, weight, and condition of the 10 patient and on the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The compounds of the present invention may be in the form of pharmaceutically acceptable salts both those which can be produced from 15 the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

Conventional forms and means for administering renin-inhibiting compounds may be employed and are described, e.g., in U.S. Patent 20 No. 4,424,207 which is incorporated by reference herein. Likewise, the amounts disclosed in the U.S. Patent No. 4,424,207 are examples applicable to the compounds of the present invention.

The compounds of the present invention are preferably orally administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration 25 include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated or solvated form.

The renin-inhibiting compounds of this invention may be administered in combination with other agents used in antihypertensive 30 therapy such as diuretics, α and/or β -adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin-converting enzyme inhibitors, and the like as described for example in published European patent application 156 318.

The compounds of the present invention are prepared as depicted in 35 the charts and as described more fully in the Preparations and Examples.

In Scheme I, treatment of the racemic γ -lactones 1 and 3 with lithium thiophoxide in hexamethylphosphoramide affords the cor-

responding acids 2 and 4, respectively. The γ -lactone 1 is obtained from the reaction of benzyl bromide with the lithium salt of γ -butyrolactone. The γ -lactone 3 is prepared as described in Preparation 2.

In Scheme II, coupling of the acid 2 and norleucine benzylester 5 gives the amide 6 as a mixture of epimers. Reaction with trimethylsilyloxonium tetrafluoroborate gives the sulfonium salt 7 which is treated with lithium salt of N-methylacetamide to give the desired γ -lactams 8a and 8b. At this point, the two epimers can be separated by column chromatography on silica gel. The individual benzylesters 8a and 8b are hydrogenolyzed to the corresponding carboxylic acids 9a and 9b, respectively.

The γ -lactam 13 building block is prepared in an analogous fashion as outlined in Scheme III, starting with the racemic acid 4. In this sequence, the carboxylic acid 13 is isolated as a mixture of epimers.

15 The reference peptide 16 is prepared as shown in Scheme IV. The previously known amine 14 (H-Leu Ψ [CHOHCH₂]Val-Ile-AMP) is extended on the N-terminus with Boc-norleucine and Boc-phenylalanine successively to give compound 16.

20 As shown in Scheme V, the separated acids 9a and 9b are individually coupled to the amine 14 to give compounds 17a and 17b, respectively.

25 The epimeric mixture of acid 13 is coupled to the amine 14 to give compound 18 as shown in Scheme VI. The benzyloxycarbonyl group is removed by hydrogenolysis and the resulting free amine is acetylated to give the peptide 19.

In the statine series, the separated acids 9a and 9b are individually coupled to the previously known amine 20 (H-Sta-Ile-AMP) to give compounds 21a and 21b, respectively, as shown in Scheme VII.

30 Generally, the renin inhibiting polypeptides may be prepared by either polymer assisted or solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. Appropriate protecting groups, reagents, and solvents for both the solution and solid phase methods can be found in "The Peptides: Analysis, Synthesis, and Biology," Vols. 1-5, eds. E. Gross and T. Meienhofer, Academic Press, NY, 1979-1983. Thus, for example, the carboxylic moiety of N^{α} -t-butyl xycarbonyl (Boc)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected

amino acid, peptide or polymer-bound peptide using a conventional coupling protocol such as dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) or diethylphosphoryl cyanide (DEPC) and triethylamine (Et_3N) in methylene chloride or dimethylformamide. The synthetic procedures used to incorporate the novel moieties herein are analogous to those described, for example, in U.S. patents 4,424,207; 4,470,971; 4,477,440; 4,477,441; 4,478,826; 4,478,827; 4,479,941; and 4,485,099, and copending application Serial No. 753,198, filed 9 July 1985, and copending application Serial No. 825,250, filed 3 February 1986, all of which are expressly incorporated by reference herein. See, also, published European patent applications 45,161; 45,665; 53,017; 77,028; 77,029; 81,783; 104,041; 111,266; 114,993; and 118,223.

Following coupling reaction completion, the N^{α} -Boc moiety may be selectively removed with 45% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropylethylamine or sodium bicarbonate in methylene chloride. In the case of polymer-assisted peptide synthesis, this stepwise, coupling strategy may be partially or completely automated to provide the desired peptide-polymer intermediates. Anhydrous hydrofluoric acid treatment of the peptide-polymer intermediate may then be used to effect simultaneous protecting group removal and cleavage of the peptide from its polymeric support. A notable exception to this includes N^{in} -formyl-indolyl-substituted peptides in which the N^{in} -formyl-indolyl moiety is stable to TFA or hydrogen fluoride but may be removed by ammonia or sodium hydroxide. Because N^{in} -formyl-tryptophane (FTrp) is somewhat unstable to base in synthetic procedures, possibly causing lower yields, it may be desirable in solution phase synthesis to introduce the FTrp-containing moiety late in the synthetic sequence so that it is not exposed to such conditions.

The incorporation of N^{in} -formyl-Trp into compounds of the present invention is easily accomplished because of the commercial availability of N^{α} -Boc- N^{in} -formyl-Trp-OH. However, the N^{in} -formyl moiety may be introduced into indolyl-substituted amino acid derivatives or related compounds by reaction with hydrochloric-formic acid as reported in the literature, see A. Previero et al, *Biochim. Biophys. Acta* 147, 453 (1967); Y.C.S. Yang et al, *Int. J. Peptide Protein Res.* 15, 130 (1980). Generally, methods of alkylation useful in alkylating histidine

for use in the present invention are found in Cheung, S.T. et al, Can. J. Chem., V 1 55, pp. 906-910 (1977). However it is now found that in the Cheung, S. T. et al, method, it is critical that the reaction conditions for the alkylation of histidine be anhydrous. 5 Further, it is now found also that during work-up instead of adding water directly to the reaction mixture, it is preferred that a buffered aqueous solution be added to the reaction mixture, for example, aqueous sodium or potassium hydrogen sulfate.

10 Variations in the above description for starting materials, reactants, reaction conditions and required protecting groups to obtain other such N-alkylated compounds are known to an ordinarily skilled chemist or are readily available in the literature.

15 The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection groups are set forth in T.W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J.F.W. McOmie, ed. Protective Groups in 20 Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (Boc), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

25 The following Preparations and Examples illustrate the present invention.

In the Preparations and Examples below and throughout this document:

- Ph is phenyl
- 30 DCC is dicyclohexylcarbodiimide
- HOBT is 1-hydroxybenzotriazole
- BOC is t-butoxycarbonyl
- DEPC is diethylphosphoryl cyanide
- TFA is trifluoroacetic acid
- 35 TEA is triethylamine
- M or mol is mole
- C is centigrade
- ml is milliliter

THF is tetrahydr furan
TLC is thin layer chromatography
EtOAc is ethyl acetate
MS is mass spectroscopy
5 IR is infra red spectra
 $^1\text{H-NMR}$ is nuclear magnetic resonance
 CDCl_3 is deuteriochloroform
HPLC is high performance liquid chromatography
MPLC is medium pressure liquid chromatography
10 g is grams
min. is minute
Me is methyl
AMP is 2-(aminomethyl)pyridinyl
Tos is p-toluenesulfonyl
15 Bn is benzylester
Bz is benzyl
Cbz is benzyloxycarbonyl.
The wedge-shape line indicates a bond which extends above the
plane of the paper relative to the plane of the compound
thereon.
20 The dotted line indicates a bond which extends below the plane of
the paper relative to the plane of the compound thereon.
Celite is a filter aid.
RIP means a compound having the formula H-Pro-His-Phe-His-Phe-
25 Phe-Val-Tyr-Lys-OH.2($\text{CH}_3\text{C}(0)\text{OH}$). XH_2O which is a known renin-
inhibiting peptide.
FTrp is $\text{N}^{\text{in}}\text{-formyl-Trp}$.
Preparation 1 2-(2-Methylthioethyl)-dihydrocinnamic acid (2). Refer
to Scheme I.
30 A mixture of 1.0326 g of 2-benzyl- γ -butyrolactone (1) and 0.64 g
of lithium thiomethoxide in 5 ml of hexamethylphosphoramide is allowed
to stir at room temperature. After 2 days, the reaction mixture is
taken up in 50 ml of water and then extracted with three 30 ml portions
of dichloromethane. The aqueous phase is acidified (methyl orange as
35 indicator) with concentrated hydrochloric acid. The resulting mixture
is extracted with three 30 ml portions of ether. The combined ethereal
phases are washed with three 20 ml portions of water. The organic
phas is then dried with magnesium sulfate and then concentrated to

give 1.25 g of the title product 2.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (δ , CDCl_3): 7.24, 2.01.

Preparation 2 α -Benzyl- α -benzyloxycarbonylamino- γ -butyrolactone (3).

5 Refer to Scheme I.

To a mixture of 3.84 g of α -amino- γ -butyrolactone hydrogenbromide in 40 ml of dichloromethane is added 2.15 ml of benzaldehyde, followed by 5.9 ml of triethylamine and excess magnesium sulfate. After stirring at room temperature for 20 hours, the mixture is filtered and 10 the filtrate concentrated. A 200 ml portion of ether is added and the resulting suspension filtered. The filtrate is washed with 50 ml of saturated aqueous sodium chloride. The aqueous phase is extracted with two 100 ml portions of ether. The combined organic phase is dried (magnesium sulfate), filtered, and then concentrated. The residue is 15 evaporatively distilled at 0.05 mmHg (Krugelrohr oven 200-250°C) to give 3.5 g of N-benzylidene- α -amino- γ -butyrolactone as an oil which solidifies on storage in a freezer: $^1\text{H-NMR}$ (δ , CDCl_3): 2.9, 4.3, 7.35, 7.7, 8.3.

To a stirred solution of 2.8 ml of diisopropylamine in 12 ml of 20 tetrahydrofuran at -78°C under argon is added 11.7 ml of n-butyllithium in hexane. After 15 min, a solution of 3.16 g of N-benzylidene- α -amino- γ -butyrolactone in 10 ml of tetrahydrofuran at -78°C under argon is cannulated into the stirred reaction mixture. After 15 min, 2.14 ml 25 of benzyl bromide is added. After 5 min, the reaction mixture is allowed to stir at room temperature for 24 hours. It is then cooled in an ice bath and 20 ml of 10% aqueous hydrogen chlorine is added. After stirring at room temperature for 1 hour, it is recooled in an ice bath and an excess of saturated aqueous sodium bicarbonate is slowly added. The resulting mixture is added to 200 ml of dichloromethane and washed 30 with 50 ml of saturated aqueous sodium bicarbonate. The aqueous phase is extracted with three 100 ml portions of dichloromethane. The combined organic phase is dried (magnesium sulfate), filtered, and then concentrated. The resulting residue is flash-chromatographed on silica gel with ethyl acetate to 5% methanol in ethyl acetate to give 1.6 g of 35 α -benzyl- α -amino- γ -butyrolactone as a yellow oil: $^1\text{H-NMR}$ (δ , CDCl_3): 1.56, 2.81, 3.03, 7.2.

To a stirred solution of 1.55 g of α -benzyl- α -amino- γ -butyrolactone in 16 ml of tetrahydrofuran is added 2.0 g of powdered sodium

-19-

carbonate, followed by 1.27 ml of benzylchloroformate. After stirring at room temperature for 18 hours, water is added to dissolve the salt and the resulting mixture is diluted with 100 ml of ethyl acetate. It is washed with 50 ml of saturated aqueous sodium chloride. The aqueous phase is extracted with two 50 ml portions of ethyl acetate. The combined organic phase is dried (magnesium sulfate), filtered, and then concentrated. The residue is passed through 20 g of silica gel with ethyl acetate, and the filtrate concentrated to the title product as a white solid, 2.6 g.

10 Physical characteristics are as follows:

$^1\text{H-NMR}$ (δ , CDCl_3): 2.67, 2.97, 3.2, 3.44, 4.15, 5.10, 5.34, 7.26, 7.34.

Anal. Found: C, 70.29; H, 5.96; N, 4.13.

MS: M/Z 234, 190, 175, 174, 91.

15 Preparation 3 2-Benzyl-N-benzyloxycarbonyl-DL-methionine (4). Refer to Scheme I.

A mixture of 2.475 g of the γ -lactone 3 of Preparation 2 and 540 mg of lithium thiomethoxide in 8 ml of hexamethylphosphoramide is allowed to stand at room temperature for 4 days. It is then added to 20 150 ml of dichloromethane and 50 ml of saturated aqueous sodium chloride. To this vigorously-stirred mixture is added 10% aqueous hydrochloric acid (methyl orange indicator) until acidic. The organic phase is further washed with 50 ml of saturated aqueous sodium chloride. The aqueous phases are extracted with the same two 60 ml portions of dichloromethane. The combined organic phase is dried with magnesium sulfate, filtered, and then concentrated. The residue is taken up in 25 200 ml of water and the aqueous phase extracted with three 200 ml portions of ether. The combined organic phase is dried with magnesium sulfate, filtered, and then concentrated to give 2.5 g of the title product 4.

30 Physical characteristics are as follows:

$^1\text{H-NMR}$ (δ , CDCl_3): 6.8-7.4, 5.5, 5.1, 3.6, 3.1, 2.1.

Preparation 4 N-[2-(2-methylthioethyl)-dihydrocinnamyl]-L-norleucyl-benzylester (6). Refer to Scheme II.

35 To a stirred solution of 5.54 mmol of the acid 2 of Preparation 1, 6.1 mmol of L-norleucyl-benzylester (5) (as a salt in dichloromethane is washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate), 0.75 g of HOBT in 50 ml of dichloromethane is added

-20-

1.25 g of DCC. After 14 hours, the reaction mixtur is filtered and the filtrate washed with aqueous sodium bicarbonate. The organic phase is dried with magnesium sulfate and then concentrated. The residue is chromatographed on silica gel to give 2 g of the title product 6.

5 Physical characteristics are as follows:

$^1\text{H-NMR}$ (δ , CDCl_3): 7.3, 5.9, 5.22, 5.05, 2.01.

IR (cm^{-1} , mull): 3312, 1724, 1639.

$[\alpha]_D = -14^\circ$ (c = 1.01, chloroform).

MS: 427.2176 (found).

10 Anal. Found: C, 70.16; H, 7.71; N, 3.28.

Preparation 5 3R-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoic acid, benzyl ester (8a) and 3S-benzyl-2-oxo-1-pyrrolidine-2S-hexanoic acid, benzyl ester (8b). Refer to Scheme II.

15 A mixture of 747 mg of the amide 6 of Preparation 4 and 272 mg of trimethyloxonium tetrafluoroborate in 7 ml of dichloromethane is allowed to stir at room temperature for 2 hours. The solution is then concentrated and dried.

20 A solution of 190 mg of N-methyl-acetamide in 15 ml of tetrahydrofuran at 0°C under argon is added 1.75 ml of lithium hexamethyl-disilazide. After 30 min, the reaction mixture is partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase is dried with magnesium sulfate and then concentrated. The residue is chromatographed on silica gel MPLC with 10% to 15% ethyl acetate in hexane to give 221 mg and 342 mg, respectively, of the title products 8a and 8b.

25 Physical characteristics are as follows:

Title product 8a:

$^1\text{H-NMR}$ (δ , CDCl_3): 7.3, 7.2, 5.2.

IR (cm^{-1} , neat): 1740, 1692.

30 $[\alpha]_D = +22^\circ$ (c = 0.525, chloroform).

MS: 379.2146 (found).

Anal. Found: C, 75.10; H, 7.74; N, 3.63.

Title product 8b:

$^1\text{H-NMR}$ (δ , CDCl_3): 7.3, 7.2, 5.2.

35 IR (cm^{-1} , neat): 1740, 1691.

$[\alpha]_D = -60^\circ$ (c = 0.658, chloroform).

MS: 379.2146 (f und).

Anal. Found: C, 75.31; H, 7.76; N, 3.32.

-21-

Preparation 6 3R-Benzyl-2-oxo-1-pyrr lidine-2S-hexanoic acid (9a).

Refer to Scheme II.

5 A suspension of 152 mg of the benzyl ester 8a of Preparation 5 and 15 mg of 10% palladium on activated charcoal in 3 ml of methanol is stirred under hydrogen at room temperature for 2 hours. The mixture is filtered and residue washed with methanol. The filtrate is combined and concentrated to give 107 mg of the title product 9a as a white solid.

Preparation 7 3S-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoic acid (9b).

10 Refer to Scheme II.

15 A suspension of 272 mg of the benzyl ester 8b of Preparation 5 and 25 mg of 10% palladium on activated charcoal in 3 ml of methanol is stirred under hydrogen at room temperature for 2 hours. The mixture is filtered and the residue washed with more methanol. The filtrate is concentrated to give 206 mg of the title product 9b as a thick oil.

Preparation 8 2-Benzyl-N-benzyloxycarbonyl-DL-methionyl-L-norleucyl-benzylester (10). Refer to Scheme III.

20 To a stirred solution of 1.43 mmol (from 562 mg of L-norleucyl-benzylester-p-toluenesulfonic acid/methylene chloride/aqueous sodium bicarbonate) of L-norleucyl-benzylester (5), 590 mg of the acid 4 of Preparation 3 and 210 mg of HOBT in 20 ml of methylene chloride is added 320 mg of DCC. After 6 hours, the mixture is filtered and the filtrate partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The organic phase is dried with magnesium sulfate and then concentrated. The residue is triturated with EtOAc and then filtered. The concentrated filtrate is chromatographed on Lobar size B column with 15% EtOAc in hexane to give the title product 10 as a white solid, 713 mg.

30 Physical characteristics are as follows:

35 $^1\text{H-NMR}$ (CDCl_3) shows approximately equal mixture of two diastereomers;

IR (cm^{-1} , mull): 1744, 1721, 1651.

$[\alpha]_D = -7^\circ$ ($c = 0.79$, chloroform).

Anal. Found: C, 68.78; H, 6.92; N, 4.78; S, 5.88.

Preparation 9 (R and S)-3-benzyl-3-benzyloxycarbonylamin-2-oxo-1-pyrrolidine-2S-hexanoic acid, benzyl esters (12). R for to Scheme III.

A mixture of 656 mg of the amide 10 of Preparation 8 and 180 mg of

-22-

trimethyloxonium tetrafluoroborate in 4.5 ml of methylene chloride is allowed to stir at room temperature for 90 min. It is then concentrated.

To a stirred solution of 125 mg of N-methyl-acetamide in 10 ml of 5 THF at 0°C is added 1.1 ml of lithium hexamethyldisilazide in THF. After 15 min a solution of the above residue in 5 ml of THF is added. After 1 hour, the reaction mixture is partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The organic phase is dried with magnesium sulfate and then concentrated. The residue is 10 flash-chromatographed on silica gel with 25% EtOAc in hexane to give 384 mg of the title product 12.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3) shows approximately equal mixture of two diastereomers.

15 IR (cm^{-1} , neat): 1738, 1697.

$[\alpha]_D = -26^\circ$ ($c = 0.789$, chloroform).

MS: 529.2695 (found).

Anal. Found: C, 72.21; H, 6.92; N, 5.02.

Preparation 10 (R and S)-3-benzyl-3-benzyloxycarbonylamino-2-oxo-1-20 pyrrolidine-2S-hexanoic acids (13). Refer to Scheme III.

To a stirred solution of 326 mg of the ester 12 of Preparation 9 in 2 ml of THF is added 1 ml of 1M aqueous sodium hydroxide and small amount of methanol to obtain a clear homogeneous solution. After 4 25 hours, THF is removed on a rotary evaporator. The aqueous phase is extracted with ether and then acidified with concentrated hydrochloric acid (methyl orange). Extractions with methylene chloride gives the title product 13 (233 mg).

Physical characteristics are as follows:

30 $^1\text{H-NMR}$ (CDCl_3) shows approximately equal mixture of two diastereomers.

IR (cm^{-1} , mull): 1720, 1643.

$[\delta]_D = -29^\circ$ ($c = 0.405$, chloroform).

MS: 439.2211 (found).

35 Anal. Found: C, 67.53; H, 6.96; N, 6.17.

Preparation 11 N-tert-butyl xycarbonyl-L-norleucyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octan yl-L-is leucyl-2-pyridyl-methylamide (15). Refer to Scheme IV.

To a stirred solution of 33.7 mg of Boc-Nle [N-tert-butyl xycarbonyl-L-norleucin] and 33.9 mg of 5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (14) in 1 ml of dichloromethane is added 0.02 ml of TEA and 0.02 ml of DEPC. After 14 hours, the suspension is partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic phase is dried with magnesium sulfate and then concentrated. The residue is chromatographed on silica gel with methylene chloride to 10% methanol in methylene chloride to give 46 mg of the title product 15.

10 Preparation 12 N-tert-butyloxycarbonyl-L-phenylalanyl-L-norleucyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (16). Refer to Scheme IV.

The peptide 15 of Preparation 11 in 0.5 ml of dichloromethane and 15 0.5 ml of TFA is allowed to stir at room temperature for 30 min. The concentrated residue is partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic phase is dried with magnesium sulfate and concentrated. The residue is dissolved in 1 ml of dichloromethane and 25 mg of N-tert-butyloxycarbonyl-L-phenylalanine 20 is added, followed by 0.015 ml of TEA and 0.015 ml of DEPC. After 14 hours, the concentrated mixture is chromatographed on silica gel with 1% to 10% methanol in methylene chloride to give 50 mg of the title product 16.

Physical characteristics are as follows:
25 HPLC (4:1 - methanol:aqueous pH 3 phosphate buffer): 6 min (retention time).

MS: 795.5395 (found).

Example 1 3R-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (17a). Refer to Scheme V.

To a stirred mixture of 20 mg of the acid 9a of Preparation 6, 20 mg of 5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl-amide (14) and 0.01 ml of TEA in 1 ml of dichloromethane is added 0.01 ml of DEPC. After 14 hours, the concentrated mixture is chromatographed on silica gel with 1% to 10% methanol in methylene chloride to give 26 mg of the title product 17a.

Physical characteristics are as follows:

HPLC (4:1 - methanol:aqueous pH 3 phosphate buffer): 7.2 min

(retention time).

MS: 706.4882 (found).

Example 2 3S-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (17b). Refer to Scheme V.

5 To a stirred mixture of 20 mg of the acid 9b of Preparation 7, 20 mg of 5S-Amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl-amide (14) and 0.01 ml of TEA in 1 ml of dichloromethane is added 0.01 ml of DEPC. After 14 hours, the concentrated mixture is 10 chromatographed on silica gel with 1% to 10% methanol in methylene chloride to give 30 mg of the title product 17b.

Physical characteristics are as follows:

HPLC (4:1 - methanol:aqueous pH 3 phosphate buffer): 6 min (retention time).

15 MS: 706.4917 (found).

Example 3 (R and S)-3-benzyl-3-benzyloxycarbonylamino-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (18). Refer to Scheme VI.

20 To a stirred solution of 57.7 mg of 5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl-amide (14), 75 mg of the acid 13 of Preparation 10 and 0.025 ml of triethylamine in 1.5 ml of dichloromethane is added 0.025 ml of DEPC. After 4 hours, the reaction mixture is concentrated and the residue is chromatographed on 25 silica gel with 5% methanol in dichloromethane to give 117 mg of the title product 18.

Physical characteristics are as follows:

HPLC (4:1 - methanol:aqueous pH 3 phosphate buffer): 8 and 10.4 min. (retention time).

30 MS: 855.5422 (found).

Example 4 (R and S)-3-benzyl-3-acetylamino-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (19). Refer to Scheme VI.

35 A mixture of 105 mg of the peptide 18 of Example 3 and 20 mg of 10% palladium/carbon in 3 ml of methanol is allowed to stir under hydrogen for 2 hours. The mixture is filtered through Celite and then concentrated to give 89 mg. The material is re-hydrated in 5 ml of

methanol (0.2 ml of acetic acid) and 20 mg of 10% palladium/carbon under 50 psi of hydr gen. After 1 day, the mixture is filtered through Celite and then concentrated. The residue is partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The 5 organic phase is dried with magnesium sulfate and then concentrated. The residue is chromatographed on silica gel with 5% methanol in methylene chloride to 5% methanol (saturated with ammonia) in methylene chloride to give 37.4 mg of (R and S)-3-benzyl-3-amino-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide.

10 To a stirred solution of 37.4 mg of (R and S)-3-benzyl-3-amino-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide, 0.004 ml of acetic acid and 0.01 ml of TEA in 0.5 ml of methylene chloride is added 0.01 15 ml of DEPC. After 3 hours, the concentrated reaction mixture is chromatographed on silica gel with EtOAc to 4% methanol in EtOAc to give the title product 19.

Physical characteristics are as follows:

HPLC (4:1 - methanol:aqueous pH 3 phosphate buffer): 4.7 and 7.2 20 min (retention time).

MS: 763.5147 (found).

Example 5 3R-benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-4S-amino-3S-hydroxy-6-methyl-heptanoyl-L-isoleucyl-2-pyridyl-methylamide (21a). Refer to Scheme VII.

25 To a stirred solution of 43.6 mg of the acid 9a of Preparation 6, 57 mg of 4S-amino-3S-hydroxy-6-methyl-heptanoyl-L-isoleucyl-2-pyridyl-methylamide (20), 0.025 ml of TEA in 1 ml of methylene chloride is added 0.025 ml of DEPC. After 14 hours, the reaction mixture is 30 concentrated and residue chromatographed on silica gel with 1% to 5% methanol in methylene chloride to give 75 mg of the title product 21a.

Physical characteristics are as follows:

HPLC (3:1 - methanol:aqueous pH 3 phosphate buffer): 8.9 min (retention time).

MS: 650.4270 (found).

35 Example 6 3S-benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-4S-amino-3S-hydroxy-6-methyl-heptanoyl-L-isoleucyl-2-pyridyl-methylamide (21b). Refer to Scheme VII.

To a stirred s lution of 134.6 mg f the acid 9b of Preparation 7,

-26-

176 mg of 4S-amin -3S-hydroxy-6-methyl-heptanoyl-L-isoleucyl-2-pyridyl-methylamide (20) and 0.07 ml of TEA in 2 ml of methylene chloride is added 0.07 ml of DEPC. After 14 hours, the mixture is concentrated and the residue chromatographed on silica gel with 1% to 5% methanol in 5 methylene chloride to give 255 mg of the title product 21b.

Physical characteristics are as follows:

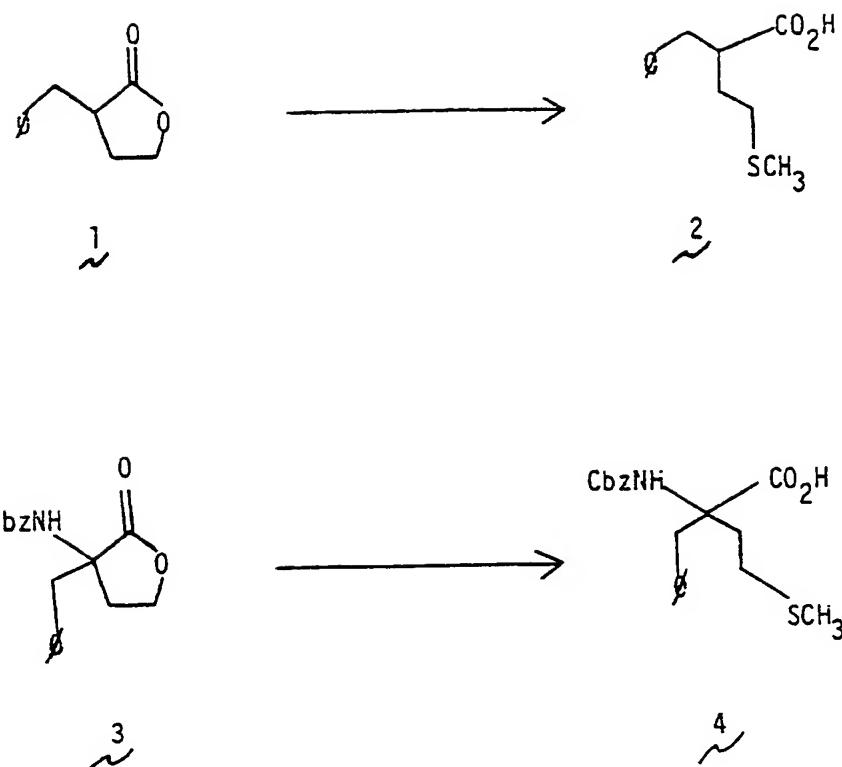
HPLC (3:1 - methanol:aqueous pH 3 phosphate buffer): 9.1 min (retention time).

MS: 650.4315 (found).

10

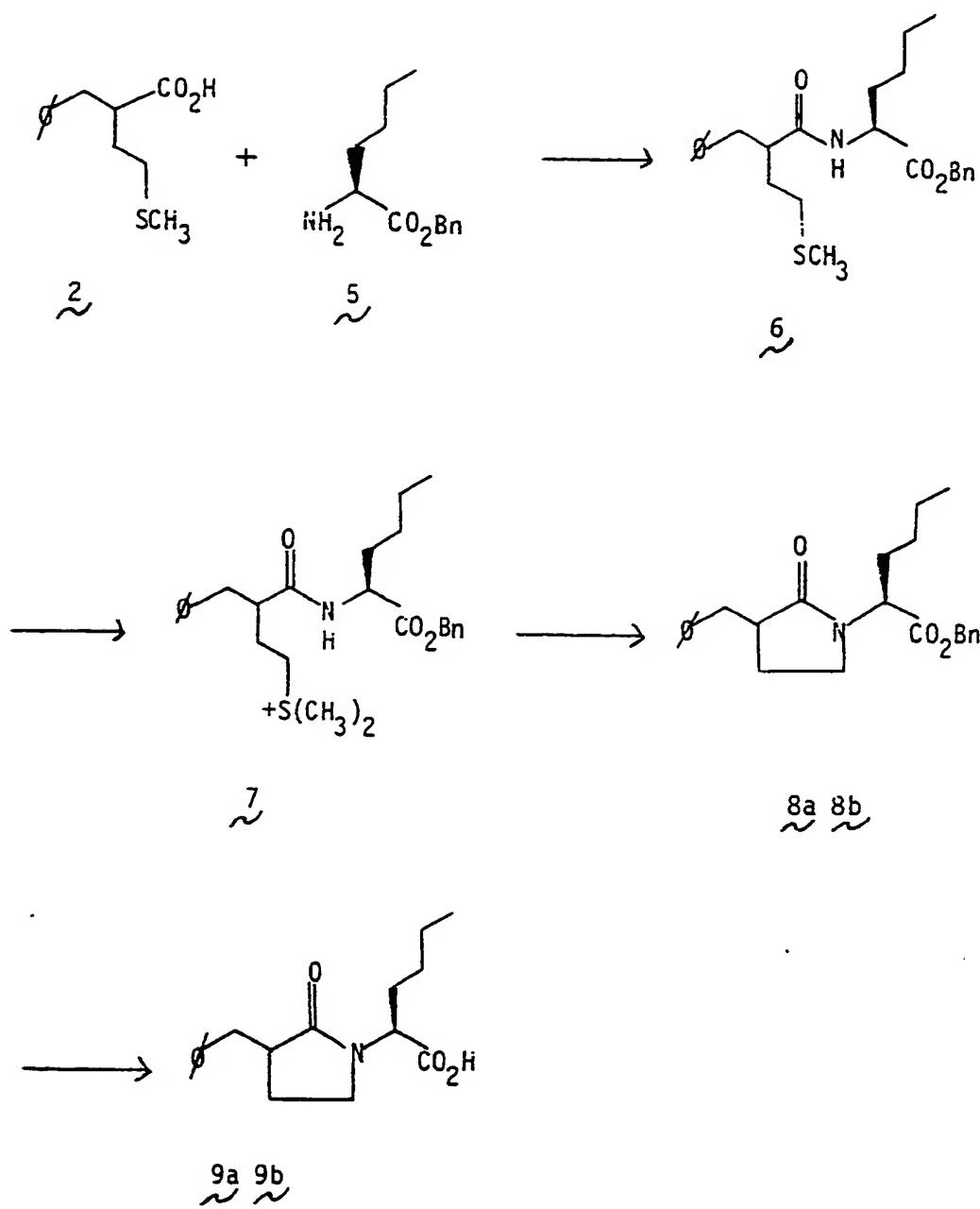
SUBSTITUTE SHEET

Scheme I

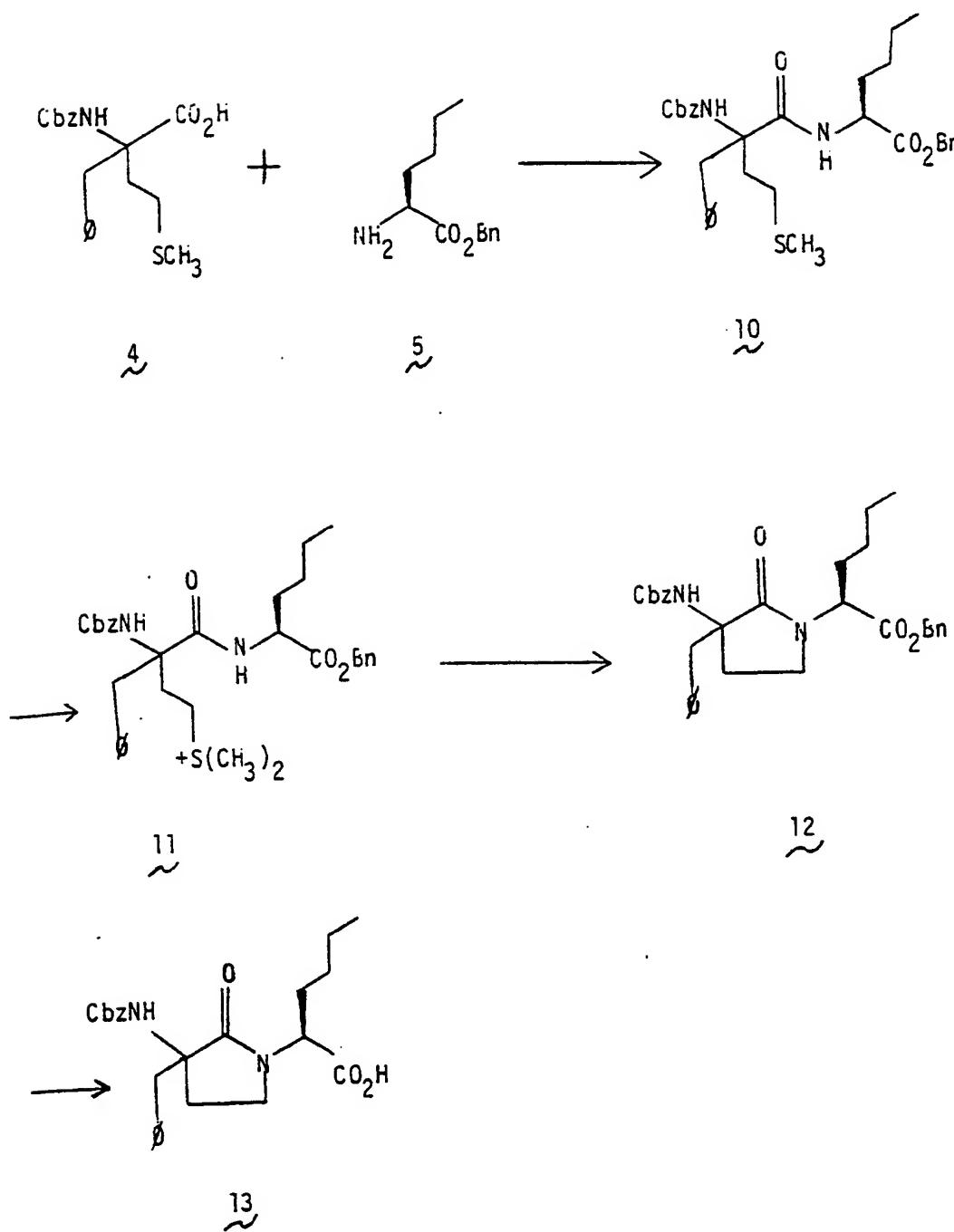


-28-

Scheme II

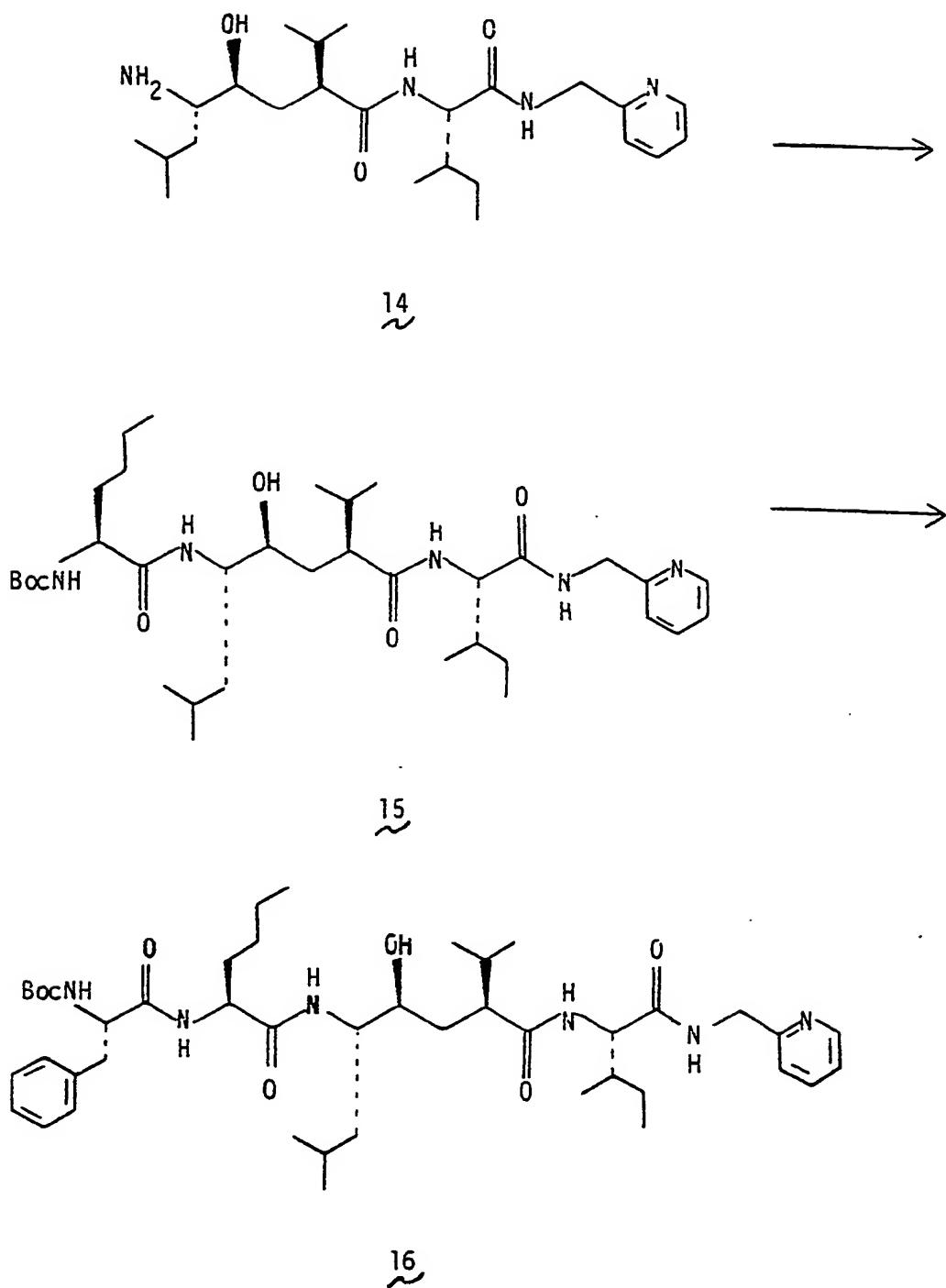


Scheme III



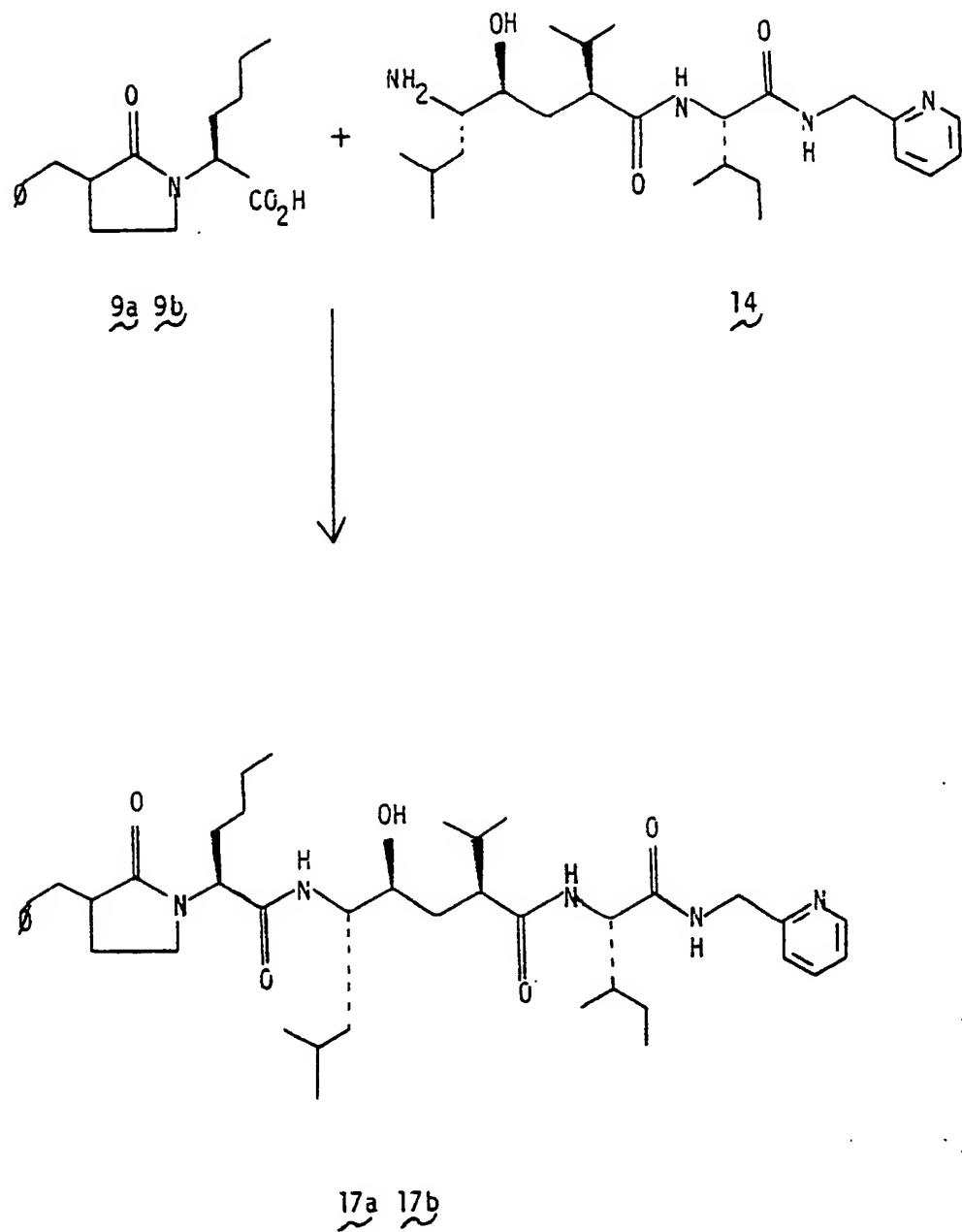
-30-

Scheme IV

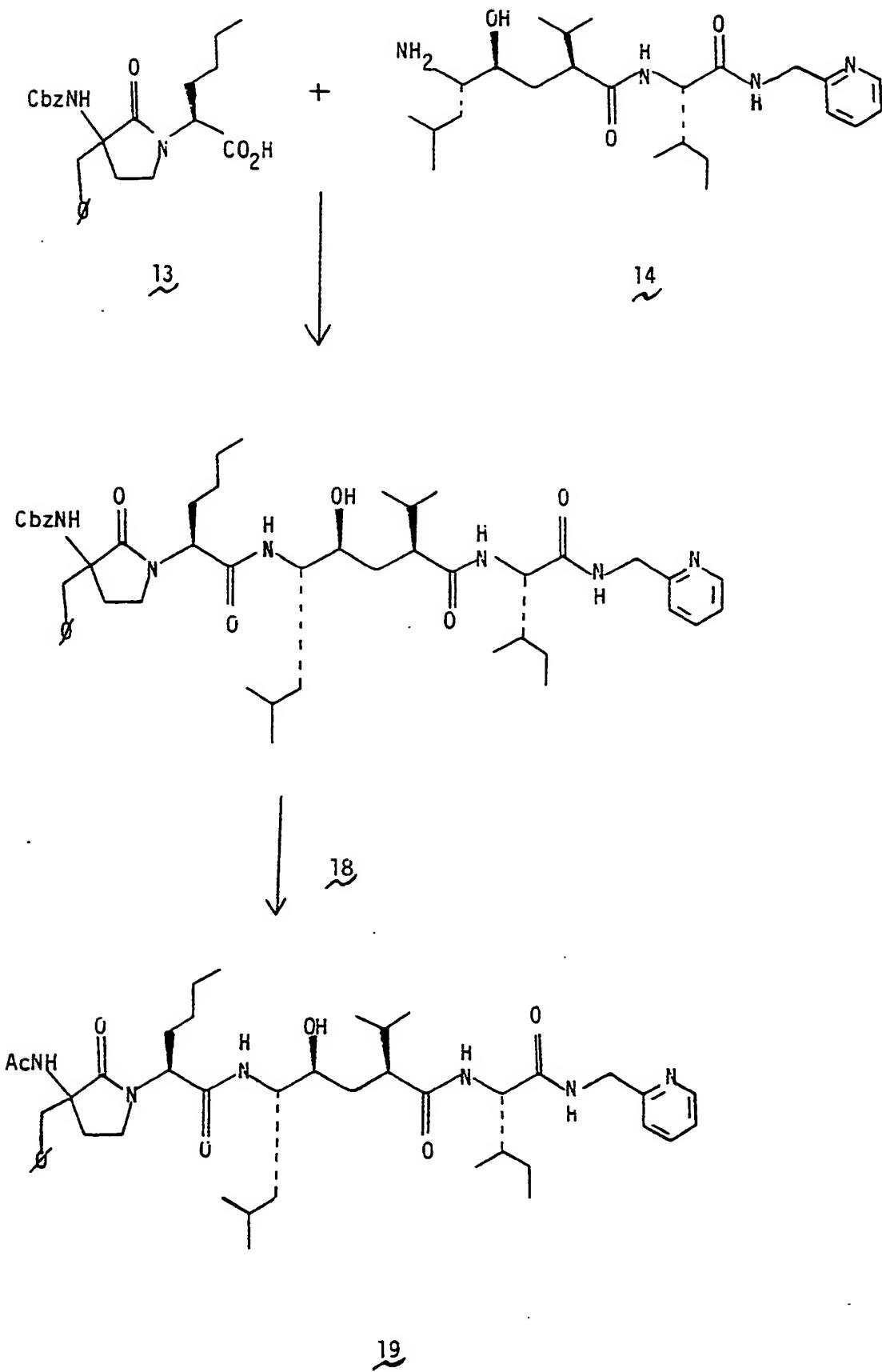


-31-

Scheme V

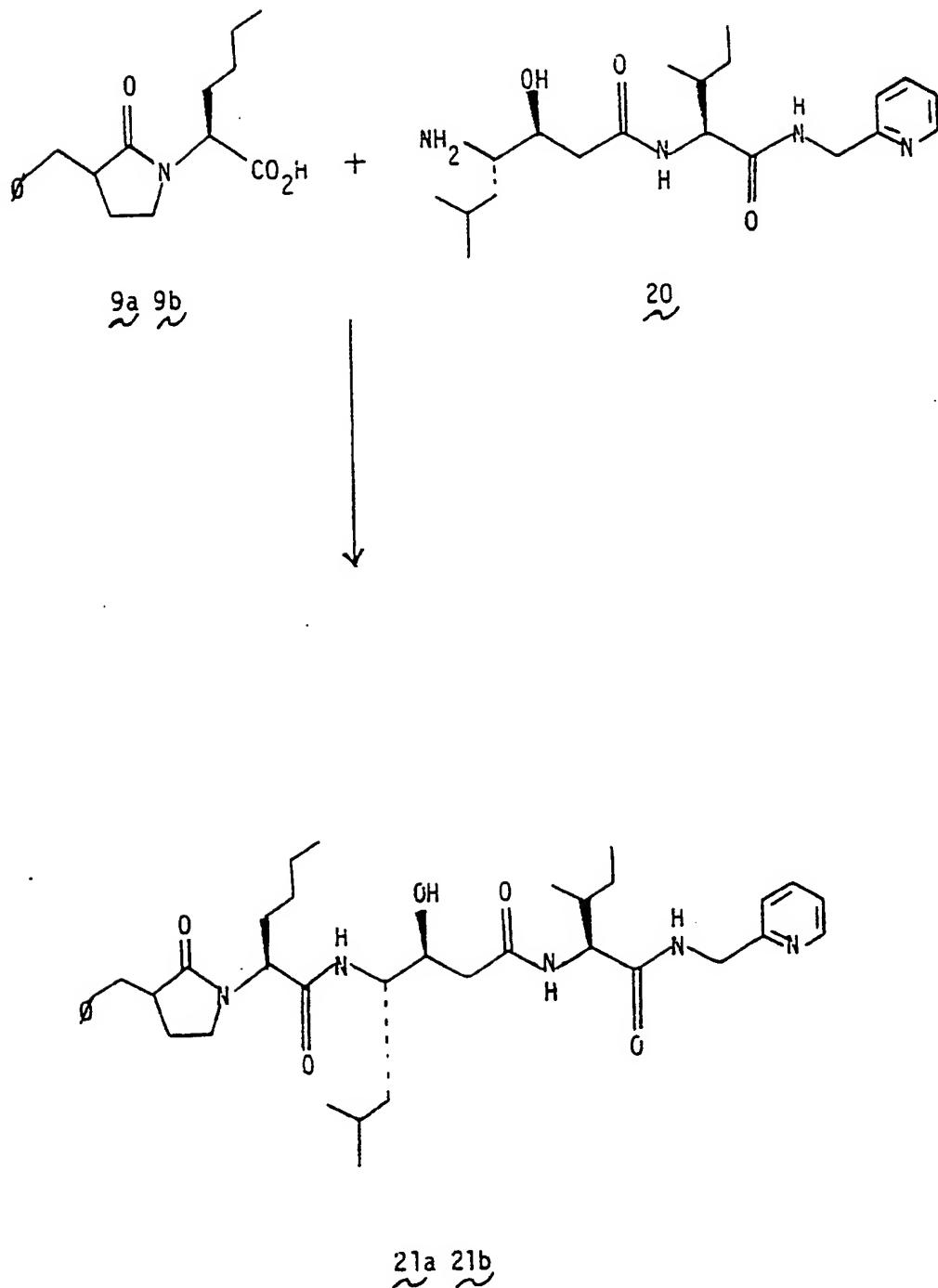


Scheme VI



-33-

Scheme VII

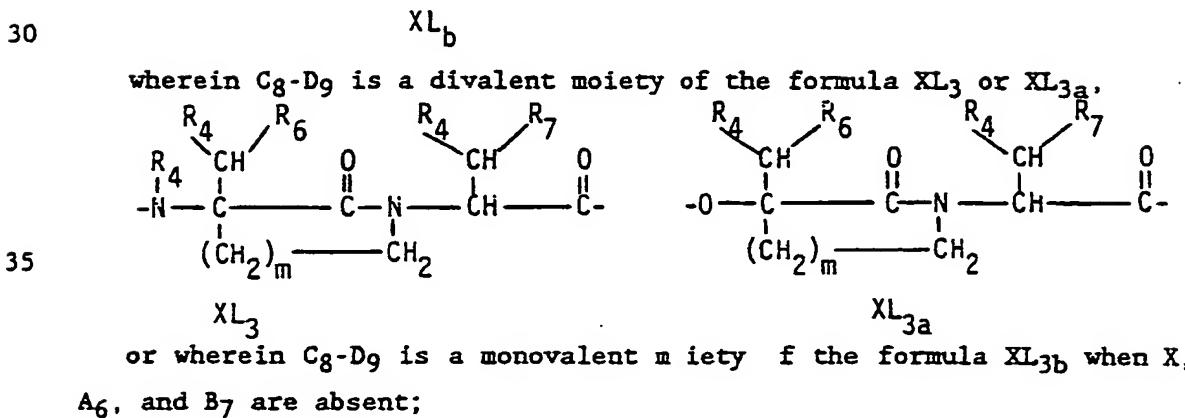
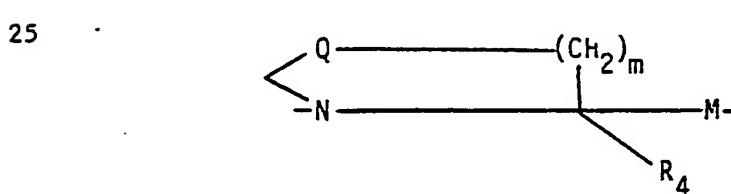
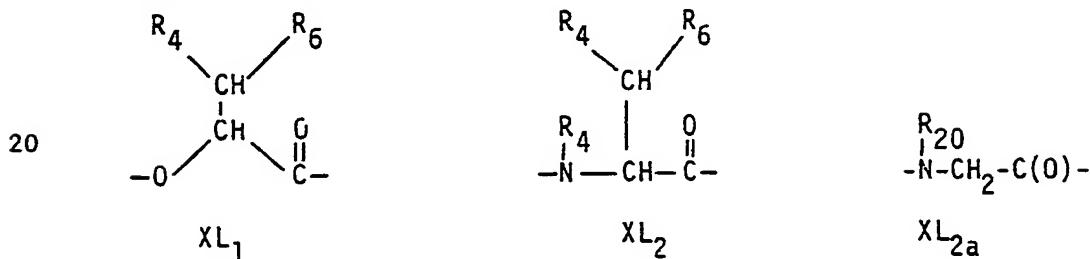


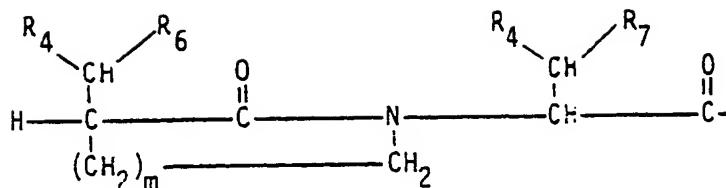
CLAIMS

1. A renin inhibitory peptide of the formula $X-A_6-B_7-C_8-D_9-E_{10}-F_{11}-G_{12}-H_{13}-I_{14}-Z$,
 wherein X is

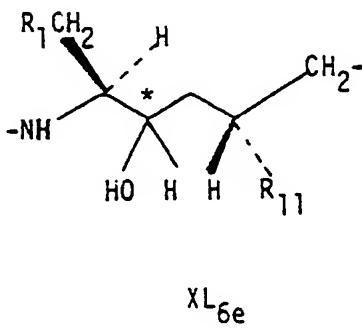
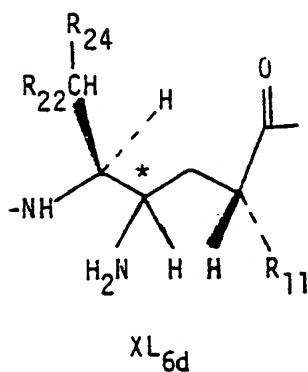
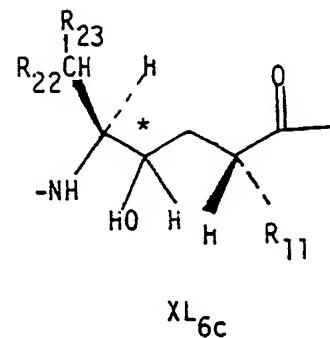
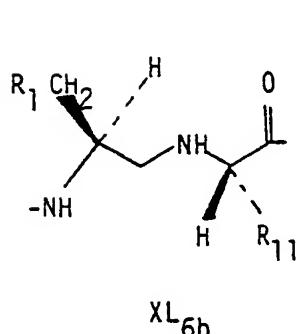
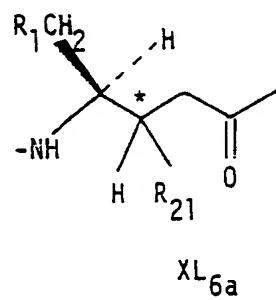
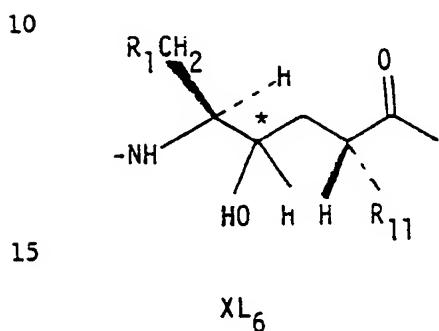
5 (a) hydrogen,
 (b) C_1-C_5 alkyl
 (c) $R_5-O-CH_2-C(O)-$,
 (d) $R_5-CH_2-O-C(O)-$,
 (e) $R_5-O-C(O)-$,
 10 (f) $R_5-(CH_2)_n-C(O)-$,
 (g) $R_4N(R_4)-(CH_2)_n-C(O)-$,
 (h) $R_5-SO_2-(CH_2)_q-C(O)-$,
 (i) $R_5-SO_2-(CH_2)_q-O-C(O)-$, or
 (j) $R_6-(CH_2)_i-C(O)-$;

15 wherein A_6 is absent or a divalent moiety of the formula XL_1 , XL_2 ,
 or XL_{2a}



 XL_{3b}

wherein $E_{10}\text{-}F_{11}$ is a divalent moiety of the formula XL_6 , XL_{6a} , XL_{6b} , XL_{6c} , XL_{6d} or XL_{6e} ;

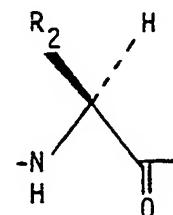
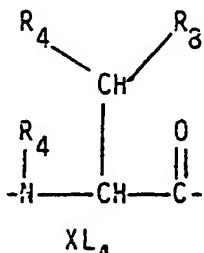


-36-

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein G_{12} is absent or a divalent moiety of the formula XL_4 or XL_{4a} ;

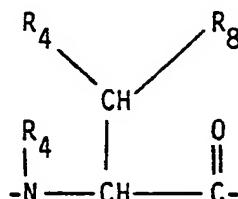
5



10

wherein H_{13} is absent or a divalent moiety of the formula XL_4 ;

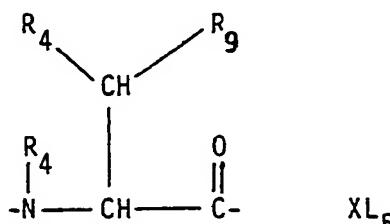
15



XL_4

wherein I_{14} is absent or a divalent moiety of the formula XL_5 ;

20



25

wherein Z is

- (a) $-O-R_{10}$,
- (b) $-N(R_4)R_{14}$, or
- (c) C_4-C_8 cyclic amino;

wherein R is

30

- (a) isopropyl,
- (b) isobutyl,
- (c) phenylmethyl, or
- (d) C_3-C_7 cycloalkyl;

wherein R_1 is

35

- (a) hydrogen,
- (b) C_1-C_5 alkyl,
- (c) aryl,
- (d) C_3-C_7 cycloalkyl,

- (e) -Het,
- (f) C_1 - C_3 alkoxy, or
- (g) C_1 - C_3 alkylthio;

wherein R_2 is

- 5 (a) hydrogen, or
- (b) - $CH(R_3)R_4$;

wherein R_3 is

- (a) hydrogen,
- (b) hydroxy,
- 10 (c) C_1 - C_5 alkyl,
- (d) C_3 - C_7 cycloalkyl,
- (e) aryl,
- (f) -Het,
- (g) C_1 - C_3 alkoxy, or
- 15 (h) C_1 - C_3 alkylthio;

wherein R_4 at each occurrence is the same or different and is

- (a) hydrogen, or
- (b) C_1 - C_5 alkyl;

wherein R_5 is

- 20 (a) C_1 - C_6 alkyl,
- (b) C_3 - C_7 cycloalkyl,
- (c) aryl,
- (d) -Het, or
- (e) 5-oxo-2-pyrrolidinyl;

25 wherein R_6 is

- (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) $-(CH_2)_p$ -aryl,
- (d) $-(CH_2)_p$ -Het,
- 30 (e) $-(CH_2)_p$ - C_3 - C_7 cycloalkyl,
- (f) 1- or 2-adamantyl,
- (g) -S-aryl,
- (h) -S- C_3 - C_7 cycloalkyl, or
- (i) -S- C_1 - C_6 -alkyl;

35 wherein R_7 is

- (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) hydroxy,

- (d) amin C_1 - C_4 alkyl-,
- (e) guanidinyl C_1 - C_3 alkyl-,
- (f) aryl,
- (g) -Het,
- 5 (h) methylthio,
- (i) $-(CH_2)_p-C_3-C_7$ cycloalkyl, or
- (j) amino;

wherein R_8 is

- 10 (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) hydroxy,
- (d) aryl,
- (e) -Het,
- (f) guanidinyl C_1 - C_3 alkyl-, or
- 15 (g) $-(CH_2)_p-C_3-C_7$ cycloalkyl;

wherein R_9 is

- 20 (a) hydrogen,
- (b) hydroxy,
- (c) amino C_1 - C_4 alkyl-, or
- (d) guanidinyl C_1 - C_3 alkyl-;

wherein R_{10} is

- 25 (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) $-(CH_2)_nR_{16}$,
- (d) $-(CH_2)_nR_{17}$,
- (e) C_3-C_7 cycloalkyl,
- (f) a pharmaceutically acceptable cation,
- (g) $-CH(R_{25})-CH_2-R_{15}$, or
- (h) $-CH_2-CH(R_{12})-R_{15}$;

30 wherein R_{11} is -R or -R₂;

wherein R_{12} is $-(CH_2)_n-R_{13}$;

wherein R_{13} is

- (a) aryl,
- (b) amino,
- 35 (c) mono-, di or tri- C_1 - C_3 alkylamino,
- (d) -Het,
- (e) C_1 - C_5 alkyl
- (f) C_3-C_7 cycloalkyl,

- (g) C_2 - C_5 alkenyl,
- (h) C_3 - C_7 cycloalkenyl,
- (i) hydroxy,
- (j) C_1 - C_3 alkoxy,
- 5 (k) C_1 - C_3 alkanoyloxy,
- (l) mercapto,
- (m) C_1 - C_3 alkylthio,
- (n) -COOH,
- (o) -CO-O- C_1 - C_6 alkyl,
- 10 (p) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
- (q) -CO-NR₂₂R₂₆;
- (r) C_4 - C_7 cyclic amino,
- (s) C_4 - C_7 cycloalkylamino,
- (t) guanidyl,
- 15 (u) cyano,
- (v) N-cyanoguanidyl,
- (w) cyanoamino,
- (x) (hydroxy C_2 - C_4 alkyl)amino, or
- (y) di-(hydroxy C_2 - C_4 alkyl)amino;

20 wherein R₁₄ is

- (a) hydrogen,
- (b) C_1 - C_{10} alkyl,
- (c) -(CH₂)_n-R₁₈,
- (d) -(CH₂)_n-R₁₉,
- 25 (e) -CH(R₂₅)-CH₂-R₁₅,
- (f) -CH₂-CH(R₁₂)-R₁₅,
- (g) (hydroxy C_1 - C_8 alkyl), or
- (h) (C_1 - C_3 alkoxy) C_1 - C_8 alkyl;

wherein R₁₅ is

- 30 (a) hydroxy,
- (b) C_3 - C_7 cycloalkyl,
- (c) aryl,
- (d) amino,
- (e) mono-, di-, or tri- C_1 - C_3 alkylamino,
- 35 (f) mono- or di-[hydroxy C_2 - C_4 alkyl]amino,
- (g) -Het,
- (h) C_1 - C_3 alkoxy-,
- (i) C_1 - C_3 alkanoyloxy-,

- (j) mercapto,
- (k) C_1 - C_3 alkylthio-,
- (l) C_1 - C_5 alkyl,
- (m) C_4 - C_7 cyclic amino,
- 5 (n) C_4 - C_7 cycloalkylamino,
- (o) C_1 - C_5 alkenyloxy,
- (p) C_3 - C_7 cycloalkenyl;

wherein R_{16} is

- 10 (a) aryl,
- (b) amino,
- (c) mono- or di- C_1 - C_3 alkylamino,
- (d) hydroxy,
- (e) C_3 - C_7 cycloalkyl,
- (f) C_4 - C_7 cyclic amino, or
- 15 (g) C_1 - C_3 alkanoyloxy;

wherein R_{17} is

- 20 (a) -Het,
- (b) C_2 - C_5 alkenyl,
- (c) C_3 - C_7 cycloalkenyl,
- (d) C_1 - C_3 alkoxy,
- (e) mercapto,
- (f) C_1 - C_3 alkylthio,
- (g) -COOH,
- (h) -CO-O- C_1 - C_6 alkyl,
- 25 (i) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
- (j) -CO-NR₂₂R₂₆,
- (k) tri- C_1 - C_3 alkylamino,
- (l) guanidyl,
- (m) cyano,
- 30 (n) N-cyanoguanidyl,
- (o) (hydroxy C_2 - C_4 alkyl)amino,
- (p) di-(hydroxy C_2 - C_4 alkyl)amino, or
- (q) cyanoamino;

wherein R_{18} is

- 35 (a) amino,
- (b) mon-, or di- C_1 - C_3 alkylamino,
- (c) C_4 - C_7 cyclic amino;
- (d) C_4 - C_7 cycloalkylamin;

wherein R_{19} is

- (a) aryl,
- (b) -Het,
- (c) tri- C_1 - C_3 alkylamino,
- 5 (d) C_3 - C_7 cycloalkyl,
- (e) C_2 - C_5 alkenyl,
- (f) C_3 - C_7 cycloalkenyl,
- (g) hydroxy,
- (h) C_1 - C_3 alkoxy,
- 10 (i) C_1 - C_3 alkanoyloxy,
- (j) mercapto,
- (k) C_1 - C_3 alkylthio,
- (l) -COOH,
- (m) -CO-O- C_1 - C_6 alkyl,
- 15 (n) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
- (o) -CO-NR₂₂R₂₆,
- (p) guanidyl,
- (q) cyano,
- (r) N-cyanoguanidyl,
- 20 (s) cyanoamino,
- (t) (hydroxy C_2 - C_4 alkyl)amino,
- (u) di-(hydroxy C_2 - C_4 alkyl)amino; or
- (v) -SO₃H;

wherein R_{20} is

- 25 (a) hydrogen,
- (b) C_1 - C_5 alkyl, or
- (c) aryl- C_1 - C_5 alkyl;

wherein R_{21} is

- (a) -NH₂, or
- 30 (b) -OH;

wherein R_{22} is

- (a) hydrogen, or
- (b) C_1 - C_3 alkyl;

wherein R_{23} is

- 35 (a) -(CH₂)_n-OH,
- (b) -(CH₂)_n-NH₂,
- (c) aryl, or
- (d) C_1 - C_3 alkyl;

wherein R_{24} is

- (a) $-R_1$,
- (b) $-(CH_2)_n-OH$, or
- (c) $-(CH_2)_n-NH_2$;

5 wherein R_{25} is

- (a) hydrogen,
- (b) C_1-C_3 alkyl, or
- (c) phenyl- C_1-C_3 alkyl;

wherein R_{26} is

- 10 (a) hydrogen,
- (b) C_1-C_3 alkyl, or
- (c) phenyl- C_1-C_3 alkyl;

wherein m is one or two;

wherein for each occurrence n is independently an integer of zero to
15 five, inclusive;

wherein p is zero to 2 inclusive;

wherein q is 1 to 5, inclusive;

wherein Q is

- 20 (a) $-CH_2-$,
- (b) $-CH(OH)-$,
- (c) $-O-$, or
- (d) $-S-$; and

wherein M is

- 25 (a) $-CO-$, or
- (b) $-CH_2-$;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the
following:

- (a) C_1-C_3 alkyl,
- (b) hydroxy,
- 30 (c) C_1-C_3 alkoxy,
- (d) halo,
- (e) amino,
- (f) mono- or di- C_1-C_3 alkylamino,
- (g) $-CHO$,
- 35 (h) $-COOH$,
- (i) $COOR_{26}$,
- (j) $CONHR_{26}$,
- (k) nitro,

- (l) mercapto,
- (m) C_1 - C_3 alkylthio,
- (n) C_1 - C_3 alkylsulfinyl,
- (o) C_1 - C_3 alkylsulfonyl,
- 5 (p) $-N(R_4)-C_1$ - C_3 alkylsulfonyl,
- (q) SO_3H ,
- (r) SO_2NH_2 ,
- (s) -CN, or
- (t) $-CH_2NH_2$;

10 wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3
15 of the following:

- (i) C_1 - C_6 alkyl,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- (iv) C_1 - C_4 alkoxy,
- 20 (v) halo,
- (vi) aryl,
- (vii) aryl C_1 - C_4 alkyl-,
- (viii) amino,
- (ix) mono- or di- C_1 - C_4 alkylamino, and
- 25 (x) C_1 - C_5 alkanoyl;

with the overall provisos that

(1) R_{18} or R_{19} is hydroxy, mercapto, or amino, or a mono-substituted nitrogen containing group bonded through the nitrogen only when n is not one;

30 (2) R_{12} is $-(CH_2)_n-R_{13}$ and n is zero and both R_{13} and R_{15} are oxygen-, nitrogen-, or sulfur-containing substituents bonded through the hetero atom, only when the hetero atom is not also bonded to hydrogen;

(3) R_{17} or R_{19} is $-COOH$ only when n for that moiety is other than
35 zero;

(4) R_{16} or R_{17} is an amin -containing substituent, hydroxy, mercapto, or -Het bonded through the hetero atom only when n for that substituent is an integer from two to five, inclusiv ;

-44-

(5) when R_{12} is $-(CH_2)_n-R_{13}$ and n is zero, then R_{13} and R_{15} cannot both be $-COOH$; and

(6) R_{17} or R_{19} is $-Het$, only when $-Het$ is other than cyclic amino; or a carboxy-, amino-, or other reactive group-protected form 5 thereof;

or a pharmaceutically acceptable acid addition salt thereof.

2. 3R-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide, a 10 compound of claim 1.

3. 3S-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide, a 15 compound of claim 1.

4. (R and S)-3-benzyl-3-benzyloxycarbonylamino-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide, a compound of claim 1.

20 5. (R and S)-3-benzyl-3-acetylamino-2-oxo-1-pyrrolidine-2S-hexanoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide, a compound of claim 1.

25 6. 3R-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-4S-amino-3S-hydroxy-6-methyl-heptanoyl-L-isoleucyl-2-pyridylmethylamide, a compound of claim 1.

30 7. 3S-Benzyl-2-oxo-1-pyrrolidine-2S-hexanoyl-4S-amino-3S-hydroxy-6-methyl-heptanoyl-L-isoleucyl-2-pyridylmethylamide, a compound of claim 1.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US87/00507</p> <p>(22) International Filing Date: 13 March 1987 (13.03.87)</p> <p>(31) Priority Application Number: 844,716</p> <p>(32) Priority Date: 27 March 1986 (27.03.86)</p> <p>(33) Priority Country: US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US Filed on 844,716 (CON) 27 March 1986 (27.03.86)</p> <p>(71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p>		<p>(72) Inventor; and (75) Inventor/Applicant (for US only): THAISRIVONGS, Suvit [TH/US]; 1327 Edington Avenue, Portage, MI 49002 (US).</p> <p>(74) Agent: COX, Martha, A.; Patent Law Department, The Upjohn Company, Kalamazoo, MI 49001 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.</p> <p>Published With international search report.</p> <p>(88) Date of publication of the international search report: 24 March 1988 (24.03.88)</p>	

(54) Title: RENIN INHIBITORS HAVING A LACTAM PSEUDO DIPEPTIDE

(57) Abstract

Novel renin-inhibiting peptides of the formula X-A₆-B₇-C₈-D₉-E₁₀-F₁₁-G₁₂-H₁₃-I₁₄-Z, having a lactam pseudo dipeptide at C₈-D₉ positions, X and Z are terminal groups, and the remaining variables are absent or are amino acid residues. Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension.

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 87/00507

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴ C 07 K 5/06; C 07 D 413/12; A 61 K 37/64; 31/41; 31/435

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
IPC ⁴	C 07 K 5/00; C 07 D 413/00; A 61 K 37/00; 31/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP, A, 0173481 (UPJOHN) 5 March 1986 see pages 148-159; claim 1	1-7
Y	EP, A, 0142335 (SQUIBB) 22 May 1985 see pages 1-17	1-7
P,Y	EP, A, 0189203 (ABBOTT) 30 July 1986 see pages 1-5	1-7

* Special categories of cited documents: ¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
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IV. CERTIFICATION

Date of the Actual Completion of the International Search
19th October 1987

Date of Mailing of this International Search Report

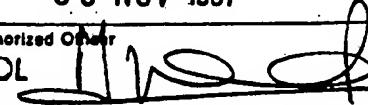
30 NOV 1987

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M. VAN MOL



ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 87/00507 (SA 16546)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/11/87.

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